

Bayesian Crossover Designs for Generalized Linear Models

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Abstract

This article discusses D-optimal Bayesian crossover designs for generalized linear models. Crossover trials with t treatments and p periods, for $t \leq p$, are considered. The designs proposed in this paper minimize the log determinant of the variance of the estimated treatment effects over all possible allocation of the n subjects to the treatment sequences. It is assumed that the p observations from each subject are mutually correlated while the observations from different subjects are uncorrelated. Since main interest is in estimating the treatment effects, the subject effect is assumed to be nuisance, and generalized estimating equations are used to estimate the marginal means. To address the issue of parameter dependence a Bayesian approach is employed. Prior distributions are assumed on the model parameters which are then incorporated into the D-optimal design criterion by integrating it over the prior distribution. Three case studies, one with binary outcomes in a 4×4 crossover trial, second one based on count data for a 2×2 trial and a third one with Gamma responses in a 3×2 crossover trial are used to illustrate the proposed method. The effect of the choice of prior distributions on the designs is also studied.

Keywords: Bayesian designs; Count data; Efficiency; Gamma response; Generalized estimating equations; Logistic regression.

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1. Introduction

Crossover designs are widely used in pharmaceutical and clinical trials, bioequivalence studies and biological assays, where the response is quite frequently non-normal (Layard and Arvesen (1978), Forster (1992), Waterhouse et al. (2006) and Bandyopadhyay et al. (2009)) and have to be modeled using a generalized linear model (GLM). While methods for analyzing GLM data arising from crossover trials are available in Senn (2002) and Jones and Kenward (2014), the question of designing such studies in an optimal manner does not seem to have been addressed before in the statistical literature. The usual practice is to extend the use of the same designs which are found to be optimal in the normal case, to these non-normal response situations.

For illustration consider an experiment where the experimenter is interested to study the effect of four treatments (A, B, C, D) on 80 subjects in four time periods. The response variable is binary in nature. The experimenter selects the four treatment sequences $\{ABCD, BDAC, CADB, DCBA\}$ forming a Williams design. For normal responses in a 4×4 crossover trial, a Williams designs has been shown to be optimal, but how does the experimenter know it is also the best design when the response is binary?

In this article, we study optimal crossover designs for GLMs. Three case studies based on non-normal responses are used to illustrate the proposed methodology. Crossover trials with t treatments and p periods, for $t \leq p$ are considered. The designs proposed in this paper minimize the log determinant of the variance of the estimator of treatment contrast of direct effects over all possible allocation of the n subjects to the treatment sequences. While analyzing data from crossover trials, the correlation between observations within subjects are modeled using a “working correlation structure”, which may be assumed to be compound symmetric or auto regressive in nature. Since the main interest is in estimating the treatment effects, the subject effects as taken as nuisance parameters and generalized estimating equations of Liang and Zeger (1986) are used to estimate the marginal means.

As in all GLM designs, the variance of the treatment effect estimator depends on the

model parameters. To address the issue of the parameter dependence and obtain robust designs we propose D-optimal Bayesian crossover designs. In our approach, a prior distribution is assumed on the model parameters, which is then incorporated into an appropriate objective function (variance of the treatment contrast) by integrating and averaging over the prior distribution. Similar to our Bayesian design criterion, an average criterion called A -criterion have been used before for crossover designs for normal responses by (Kempton et al. (2001), Baily and Kunert (2006), Zheng (2013) and Li et al. (2015)). Bayesian designs have been a popular choice whenever the variance-covariance matrix depends on the model parameters, for some references see (Chaloner and Larntz (1989), Dette and Sperlich (1994), Woods and Peter (2011) and Mylona et al. (2014)).

2. Case studies

For illustration purpose we consider three case studies based on crossover trials involving binary, count and Gamma responses.

2.1. A four periods four treatments binary response crossover trial

The first case study presented here is from a trial based on the four-period, four treatment Williams design. It has been reported in Kenward and Jones (1992). The four treatments are denoted by A, B, C and D. Eighty subjects are randomly assigned to the four treatment sequences $\{ABCD, BDAC, CADB, DCBA\}$, with about twenty subjects allocated to each treatment sequence. The response is a binary outcome taking values 1 and 0 based on patient relief and no relief, respectively.

The research question which arises from the above case study is why did the experimenter select the 4 treatment sequences $\{ABCD, BDAC, CADB, DCBA\}$ forming a Williams design (Williams (1949)). Is this the best possible selection of treatment sequences? The book by Bose and Dey (2009), page 40 shows that for normal response crossover models, for the 4 treatment and 4 periods case, Williams design is the optimal design. But how can we be sure that the same design applies to a binary response crossover framework as well? Does

the selected design change if the correlation structure between observations change say, from equicorrelated to auto regressive structure?

2.2. Two periods two treatments Poisson response crossover trial

This study is based on an example described in Layard and Arvesen (1978). Two drugs, standard drug A and an innovation drug B, is administered for controlling angina in 20 patients. It is known that the innovative drug B is no worse than the standard drug A. For a given patient, number of angina attacks on weekly basis is assumed to follow a Poisson distribution (Layard and Arvesen (1978)). Number of attacks for each patient of consecutive two weeks are recorded. Treatment sequences considered are $\{AB, BA\}$ and 10 patients are assigned to each of the treatment sequences. This is a 2-treatments 2-periods crossover trial.

As in case study I, the question arises how does the experimenter choose the design AB, BA . Is this the best or most efficient design under the repeated measures setup when responses follow a Poisson distribution?

2.3. Three periods two treatments Gamma response trial

The length of hospital stay is an important measure of the success of hospital activity, costs incurred by patients and the treatment administered to a patient. However, its empirical distribution is often right skewed and a Gamma distribution with a log link has been seen to be a good fit (Faddy et al. (2009)). In this case study we consider a crossover trial where two treatments are applied over three periods and length of hospital stay, assumed to having a Gamma distribution, is the primary end point.

As in the earlier two case studies, we investigate the best design for a two treatment three periods design with a gamma response.

3. The model

We consider experiments where there are t treatments and n subjects, and p repeated measurements are taken from each subject. The observations from each subject may be correlated. The marginal distribution of the response Y_{ij} is described by a working generalized linear model with the following three components (Liang and Zeger (1986)):

1. Y_{ij} has a distribution from the exponential family form,

$$f(y_{ij}|\phi_{ij}, \phi) = \exp \{[y_{ij}\phi_{ij} - b(\phi_{ij}) + c(y_{ij})]\psi + d(y_{ij}, \psi)\} \quad (1)$$

where $b(\cdot)$, $c(\cdot)$ and $d(\cdot)$ are known functions and ψ is the dispersion parameter. It can be shown that: $E(Y_{ij}) = \mu_{ij} = \frac{db(\phi_{ij})}{d\phi_{ij}}$ and $Var(Y_{ij}) = \frac{d^2b(\phi_{ij})}{d\phi_{ij}^2}$.

2. The linear predictor η_{ij} in a repeated measures setup can be written as (Bose and Dey (2009)),

$$\eta_{ij} = \mu + \beta_i + \tau_{d(i,j)} + \rho_{d(i-1,j)}; \quad i = 1 \dots, p, \quad j = 1, \dots, n, \quad (2)$$

where β_i represents the effect of the i th period, τ_s is the direct effect due to treatment s and ρ_s is the carryover effect due to treatment s , $s = 1, \dots, t$.

3. The mean of y_{ij} denoted by μ_{ij} is related to η_{ij} through a link function g , where $g(\mu_{ij}) = \eta_{ij}$ and the inverse of g exists.

3.1. Estimation

Regression coefficients as well as their variances are estimated by the GEE approach of Liang and Zeger (1986) and Zeger et al. (1988). Due to observations from the same subject being correlated, a “working correlation” matrix, $R(\alpha)$, is used to describe the dependencies between repeated observations from a subject. Here, α is a vector of length s . For cases where $R(\alpha)$ is the true correlation matrix of $Y_j = (Y_{1j}, \dots, Y_{pj})'$, the covariance of Y_j is

$$V_j = A_j^{1/2} R(\alpha) A_j^{1/2}, \quad (3)$$

$A_j = \text{diag}(\text{Var}(Y_{1j}), \dots, \text{Var}(Y_{pj}))$ and $\text{Var}(Y_{ij})$ denotes the variance of Y_{ij} . Also, the asymptotic variance for the GEE estimator $\hat{\boldsymbol{\theta}}$ (see Zeger et al. (1988), equation (3.2)) is

$$\text{Var}(\hat{\boldsymbol{\theta}}) = \left[\sum_{j=1}^n \frac{\partial \mu'_j}{\partial \boldsymbol{\theta}} V_j^{-1} \frac{\partial \mu_j}{\partial \boldsymbol{\theta}} \right]^{-1}, \quad (4)$$

where $\boldsymbol{\theta} = (\mu, \boldsymbol{\beta}', \boldsymbol{\tau}', \boldsymbol{\gamma}')'$, $\boldsymbol{\beta}' = (\beta_1, \dots, \beta_p)$, $\boldsymbol{\tau}' = (\tau_1, \dots, \tau_t)$ and $\boldsymbol{\gamma}' = (\gamma_1, \dots, \gamma_t)$.

However, if the true correlation structure varies from the “working correlation” structure, then $\text{Var}(\hat{\boldsymbol{\theta}})$ is given by the sandwich formula (Zeger et al. (1988), equation (3.2))

$$\text{Var}(\hat{\boldsymbol{\theta}}) = \left[\sum_{j=1}^n \frac{\partial \mu'_j}{\partial \boldsymbol{\theta}} V_j^{-1} \frac{\partial \mu_j}{\partial \boldsymbol{\theta}} \right]^{-1} \left[\sum_{j=1}^n \frac{\partial \mu'_j}{\partial \boldsymbol{\theta}} V_j^{-1} \text{Cov}(Y_j) V_j^{-1} \frac{\partial \mu_j}{\partial \boldsymbol{\theta}} \right] \left[\sum_{j=1}^n \frac{\partial \mu'_j}{\partial \boldsymbol{\theta}} V_j^{-1} \frac{\partial \mu_j}{\partial \boldsymbol{\theta}} \right]^{-1}. \quad (5)$$

For the crossover model (1), the i th element of $\frac{\partial \mu_j}{\partial \boldsymbol{\theta}}$ is $\frac{\partial \mu_{ij}}{\partial \boldsymbol{\theta}} = x'_{ij} \frac{\partial g^{-1}(\eta_{ij})}{\partial \eta_{ij}}$, where x'_{ij} is the i th row of X_j for $i = 1, \dots, p$. The design matrix is $X_j = [1_p \ P_j \ T_j \ F_j]$, where $P_j = I_p$; $T = (T'_1, \dots, T'_n)'$, where T_j is a $p \times t$ matrix with its (i, s) th entry equal to 1 if subject j receives the direct effect of the treatment s in the i th period and zero otherwise; $F = (F'_1, \dots, F'_n)'$, where F_j is a $p \times t$ matrix with its (i, s) th entry equal to 1 if subject j receives the carryover effect of the treatment s in the i th period and zero otherwise.

3.2. Specific Case: Bernoulli Distribution

If $Y_{ij} \sim \text{Bernoulli}(\mu_{ij})$, then the probability mass function of Y_{ij} is:

$$f(y_{ij}) = \exp \left\{ y_{ij} \log \frac{\mu_{ij}}{1 - \mu_{ij}} + \log(1 - \mu_{ij}) \right\}$$

Comparing with equation (1), we get $\phi_{ij} = \log \frac{\mu_{ij}}{1 - \mu_{ij}}$, $b(\phi_{ij}) = -\log(1 - \mu_{ij}) = \log(1 + \exp(\phi_{ij}))$, $c(y_{ij}) = 0$, $d(y_{ij}, \psi) = 0$ and $\psi = 1$. The mean of Y_{ij} is $E(Y_{ij}) = \mu_{ij} = \frac{\exp(\phi_{ij})}{1 + \exp(\phi_{ij})}$, and $\text{Var}(Y_{ij}) = \mu_{ij}(1 - \mu_{ij})$.

Considering the logit link function to relate the linear predictor η_{ij} to the mean μ_{ij} , $g(\mu_{ij}) = \log \frac{\mu_{ij}}{1 - \mu_{ij}}$. Thus $g^{-1}(\eta_{ij}) = \frac{e^{\eta_{ij}}}{1 + e^{\eta_{ij}}}$, and the i th component of $\frac{\partial \mu_j}{\partial \boldsymbol{\theta}}$ is $\frac{\partial \mu_{ij}}{\partial \boldsymbol{\theta}} = x'_{ij} \frac{\partial g^{-1}(\eta_{ij})}{\partial \eta_{ij}} =$

$$x'_{ij} \frac{e^{\eta_{ij}}}{(1+e^{\eta_{ij}})^2} = x'_{ij} \mu_{ij} (1 - \mu_{ij}).$$

3.3. Specific Case: Poisson Distribution

If $Y_{ij} \sim \text{Poisson}(\mu_{ij})$, then the probability mass function of Y_{ij} is:

$$f(y_{ij}) = \exp \{y_{ij} \log \mu_{ij} - \mu_{ij} - \log y_{ij}!\}$$

Comparing with equation (1), we get $\phi_{ij} = \log(\mu_{ij})$, $b(\phi_{ij}) = \mu_{ij}$, $c(y_{ij}) = -\log y_{ij}!$, $d(y_{ij}, \psi) = 0$ and $\psi = 1$. The mean of Y_{ij} is $E(Y_{ij}) = \mu_{ij} = e^{\phi_{ij}}$ and $\text{Var}(Y_{ij}) = e^{\phi_{ij}} = \mu_{ij}$.

Using the log link we obtain, $g(\mu_{ij}) = \log(\mu_{ij}) = \eta_{ij}$, and the i th component of $\frac{\partial \mu_j}{\partial \theta}$ is $\frac{\partial \mu_{ij}}{\partial \theta} = x'_{ij} \frac{\partial g^{-1}(\eta_{ij})}{\partial \eta_{ij}} = x'_{ij} e^{\eta_{ij}} = x'_{ij} \mu_{ij}$.

3.4. Specific Case: Gamma Distribution

If $Y_{ij} \sim \text{Gamma}(\kappa, \lambda_{ij})$, where $\kappa > 0$ is the shape parameter (assume it is known) and $\lambda_{ij} > 0$ is the rate parameter. Then the probability density function of Y_{ij} is:

$$f(y_{ij}) = \exp \left\{ \frac{y_{ij} \left(-\frac{\lambda_{ij}}{\kappa} \right) + \log \lambda_{ij} + \log y_{ij}}{1/\kappa} - \log y_{ij} - \log \Gamma \kappa \right\}$$

Comparing with equation (1), we get $\phi_{ij} = -\frac{\lambda_{ij}}{\kappa}$, $b(\phi_{ij}) = -\log(\lambda_{ij})$, $c(y_{ij}) = \log y_{ij}$, $d(y_{ij}, \psi) = -\log y_{ij}(\Gamma \kappa)$ and $\psi = 1/\kappa$. The mean of Y_{ij} is $E(Y_{ij}) = \mu_{ij} = \kappa/\lambda_{ij}$ and $\text{Var}(Y_{ij}) = \frac{\kappa}{\lambda_{ij}^2}$.

As in the case of Poisson distribution we use a log link function, $g(\mu_{ij}) = \log(\mu_{ij}) = \eta_{ij}$. The i th component of $\frac{\partial \mu_j}{\partial \theta}$ is $\frac{\partial \mu_{ij}}{\partial \theta} = x'_{ij} \frac{\partial g^{-1}(\eta_{ij})}{\partial \eta_{ij}} = x'_{ij} e^{\eta_{ij}} = x'_{ij} \mu_{ij}$.

4. Approximate Designs

For finding optimal crossover designs for the logistic model we use the approximate theory as in Laska et al. (1983) and Kushner (1997, 1998). Suppose Ω is the set of treatment sequences of the form $\omega = (t_1, \dots, t_p)'$, $t_i \in \{1, \dots, t\}$, and n_ω is the number of subjects

assigned to sequence ω . Then, $n = \sum_{\omega \in \Omega} n_{\omega}$, $n_{\omega} \geq 0$. A design ζ in approximate theory is specified by the set $\{p_{\omega}, \omega \in \Omega\}$ where $p_{\omega} = n_{\omega}/n$, is the proportion of subjects assigned to treatment sequence ω .

The matrices T_j and F_j depend only on the treatment sequence ω to which the j th subject is assigned, so $T_j = T_{\omega}$, $F_j = F_{\omega}$, implying, $X_j = X_{\omega}$. Thus, the variance of $\hat{\boldsymbol{\theta}}$ is

$$Var_{\zeta}(\hat{\boldsymbol{\theta}}) = \left[\sum_{\omega \in \Omega} np_{\omega} \frac{\partial \mu'_{\omega}}{\partial \boldsymbol{\theta}} V_{\omega}^{-1} \frac{\partial \mu_{\omega}}{\partial \boldsymbol{\theta}} \right]^{-1} \left[\sum_{\omega \in \Omega} np_{\omega} \frac{\partial \mu'_{\omega}}{\partial \boldsymbol{\theta}} V_{\omega}^{-1} Cov(Y_{\omega}) V_{\omega}^{-1} \frac{\partial \mu_{\omega}}{\partial \boldsymbol{\theta}} \right] \left[\sum_{\omega \in \Omega} np_{\omega} \frac{\partial \mu'_{\omega}}{\partial \boldsymbol{\theta}} V_{\omega}^{-1} \frac{\partial \mu_{\omega}}{\partial \boldsymbol{\theta}} \right]^{-1}. \quad (6)$$

If the true correlation of Y_j is equal to $R(\alpha)$ then we have a much simpler form,

$$Var_{\zeta}(\hat{\boldsymbol{\theta}}) = \left[\sum_{\omega \in \Omega} np_{\omega} \frac{\partial \mu'_{\omega}}{\partial \boldsymbol{\theta}} V_{\omega}^{-1} \frac{\partial \mu_{\omega}}{\partial \boldsymbol{\theta}} \right]^{-1}. \quad (7)$$

4.1. Design criterion

In repeated measures trials when the interest is in only estimating direct treatment effect contrasts, we may instead work with $Var(\hat{\boldsymbol{\tau}})$ given by,

$$Var_{\zeta}(\hat{\boldsymbol{\tau}}) = E Var_{\zeta}(\hat{\boldsymbol{\theta}}) E', \quad (8)$$

where E is a $t \times m$ matrix given by $[0_{t1}, 0_{tp}, I_t, 0_{tt}]$ and m is the total number of parameters in $\boldsymbol{\theta}$.

For obtaining D-optimal designs the function

$$\Lambda(\zeta, \boldsymbol{\theta}, \alpha) = \log \text{Det}(Var_{\zeta}(\hat{\boldsymbol{\tau}})). \quad (9)$$

is minimized with respect to the design ζ . Since it is a GLM the variance depends on the model parameters as well as the covariance parameters, and the design obtained is locally optimal.

To obtain D-optimal designs robust to uncertainties in the parameters we propose a

Bayesian approach. This method has been used before for logistic regression by Chaloner and Larntz (1989), and Dror and Steinberg (2006) and for block designs by Woods and Peter (2011). For repeated measures models, the design which minimizes

$$\Psi(\mathfrak{B}, \zeta, \alpha) = \int_{\mathfrak{B}} \Lambda(\zeta, \boldsymbol{\theta}, \alpha) dF(\boldsymbol{\theta}), \quad (10)$$

where $\mathfrak{B} \subset \mathbb{R}^m$ is the parameter space of parameter vector $\boldsymbol{\theta}$ and $F(\boldsymbol{\theta})$ is a proper prior distribution for $\boldsymbol{\theta}$, is the D -optimal Bayesian crossover design. Note, no prior distributions are assigned to the correlation parameters α , designs are obtained only for some fixed values chosen for α .

In our computations we have used both uniform and normal priors for $\boldsymbol{\theta}$. The minimization of the objective function in (10) with respect to ζ , requires high-dimensional integral calculation. In a GEE setup with blocks, Woods and Peter (2011) uses Latin Hypercube Sampling (LHS) for deriving an approximate solution of the above optimization problem. For uniform priors, we use the average of (10) across 100-point discrete samples using LHS as the approximate solution of (10). When $\boldsymbol{\theta}$ has a Gaussian distribution, Latin Hypercube Sampling from Gaussian fields is used (for more details see Stein (1987)).

For evaluating the performance of design ζ with respect to the reference design ζ^* (D-optimal Bayesian design), we use the D-efficiency criterion defined as:

$$Eff_D(\zeta, \zeta^*, \mathfrak{B}, \alpha) = \left(\frac{\Psi(\mathfrak{B}, \zeta^*, \alpha)}{\Psi(\mathfrak{B}, \zeta, \alpha)} \right)^{1/m}, \quad (11)$$

here m is the number of model parameters.

Working correlation matrix structures such as the compound symmetric (or equi-correlated) and the AR(1) are investigated. Under the equi-correlated covariance structure, $R_j = (1 - \alpha)I_p + \alpha J_p$, and under the AR(1) assumption, $R_j = \alpha^{|i-i'|}$, $i \neq i'$.

5. Examples

5.1. Example 1: Four periods, four treatments binary response trial

In Case study 1, a four periods four treatments crossover trial described in Kenward and Jones (1992) is considered. There are eighty subjects allocated to the four treatment sequences, with about twenty subjects per sequence. Treatments are denoted by A , B , C and D . The treatment sequences form a *Williams design* given as follows:

$$\begin{bmatrix} A & B & C & D \\ B & D & A & C \\ C & A & D & B \\ D & C & B & A \end{bmatrix}$$

The response variable is binary in nature. The data set is available in Table 3 of Kenward and Jones (1992). For a four periods, four treatments trial, there are 24 possible *Latin square designs* (LSDs) with every treatment represented once and only once in each row and in each column (see Table 5.1 Senn (2002)). A special form of *Latin square design* is called *Williams square design* (WSD) in which every treatment follows every other treatment only once. For normal response when $t = p$ and t is even, for reduced models LSD and for full models WSD are variance balanced designs (Lawson (2014), page 361). However, these designs may not be optimal in general. But under some subject constraints WSD is universally optimal for even t , $n \leq t(t+2)/2$ and $4 \leq t \leq 12$ (Bose and Dey (2009), page 40).

The linear predictor η_{ij} where i stands for period and j for subjects is modeled using several dummy variables as,

$$\eta_{ij} = \mu + \beta_1^* P_1 + \beta_2^* P_2 + \beta_3^* P_3 + \tau_1^* T_1 + \tau_2^* T_2 + \tau_3^* T_3 + \rho_1^* C_1 + \rho_2^* C_2 + \rho_3^* C_3, \quad (12)$$

where P_i is the indicator variable for i th period, T_k is the indicator variable for k th direct treatment effect and C_k is the indicator variable for k th carryover effect.

Point estimates and corresponding confidence intervals of the parameters are calculated using *PROC GENMOD* procedure in SAS software Inc. (1999). Results are summarized in Table 1 for both reduced and full models. In a reduced model it is assumed that there are no carryover treatment effect, while in a full model both direct and carryover treatment effects are assumed to be present. The working correlation structure is taken to be compound symmetric (CS) in nature, the correlation coefficient is estimated to be 0.215.

Table 1: Point estimates and confidence intervals for binary data in Example 1.

Parameter	Point estimate [95%Confidence interval]	
	no carryover effect	with carryover effect
μ	1.0980 [0.4232 1.7728]	1.0158 [0.3474 1.6842]
β_1^*	-0.3056 [-0.8643 0.2532]	-0.5525 [-1.2565 0.1515]
β_2^*	-0.2414 [-0.8228 0.3399]	-0.4842 [-1.2034 0.2349]
β_3^*	0.3817 [-0.2391 1.0026]	0.1234 [-0.6888 0.9356]
τ_1^*	-0.3270 [-0.8660 0.2119]	-0.2564 [-0.8075 0.2948]
τ_2^*	-0.0681 [-0.6996 0.5635]	0.0069 [-0.6473 0.6610]
τ_3^*	-0.5322 [-1.1684 0.1041]	-0.3736 [-1.0165 0.2693]
ρ_1^*	-	0.1786 [-0.5965 0.9538]
ρ_2^*	-	0.2242 [-0.5443 0.9927]
ρ_3^*	-	0.6620 [-0.1352 1.4591]

Using the parameter estimates and confidence intervals in Table 1, we determine the Bayesian crossover design by minimizing formula 10, and denote it by D^B . Instead of searching over all possible treatment sequences (4^4), the search space Ω , is restricted to 16 sequences $\{ACDB, BDCA, CBAD, DABC, ADCB, BCDA, CABD, DBAC, AABB, BBAA, CCDD, DDCC, AAAB, BBBA, CCCD, DDDC\}$. These sequences are so chosen that they can be used to form LSDs (including WSDs) and also non LSDs.

We use two types of priors for the regression parameters, the uniform and the normal. For the uniform prior, direct product of the confidence intervals of the parameter estimates in Table 1 is used to represent the parameter space \mathcal{B} . While, for the two normal priors the parameter estimates are used in the mean vector and the correlation matrix is assumed to have an independent structure with variances 0.25 and 0.50, respectively. We use $\alpha = 0.1, 0.2, 0.4, 0.6, 0.8$.

The performance of D^B is compared with 24 LSDs including 6 WSDs, and 24 extra period designs (EPDs) (a design in which first three rows correspond to a LSD and the last row is same as the previous one (Patterson and Lucas (1959))). We noted that the performance of each LSD is same among the 18 LSDs under the reduced and full models for both of the correlation structures and priors used. Same is true for 6 WSDs and 24 EPDs. Thus the results are based on one LSD, one WSD and one EPD.

5.1.1. Reduced model: No carryover effects

Under the independent correlation structure ($\alpha = 0$), D^B utilizes all the 16 sequences with equal proportions. Under CS structure, for small values of α , 70% weightage is given to the sequences forming a LSD. As α increases, however, D^B utilizes the sequences $\{ADCB, BCDA, CBAD, DABC\}$ forming a LSD with almost 100% weight and with equal proportions. Under the AR(1) structure, D^B uses only the first eight sequences with equal proportions. From Figure 1, it is noted that under CS structure both LSD and WSD are as good as D^B , while EPD performs badly. Efficiencies of LSD and WSD are constant with respect to α . Under the AR(1) structure, WSD is most efficient followed by LSD, and EPD performs worst. Note that performance of LSD and EPD designs decrease as α increases.

5.1.2. Full model: With carryover effect

For $\alpha = 0$, D^B utilizes the first eight sequences with equal proportions and more than 80% weight. Under the CS structure, D^B utilizes the first eight sequences with more than

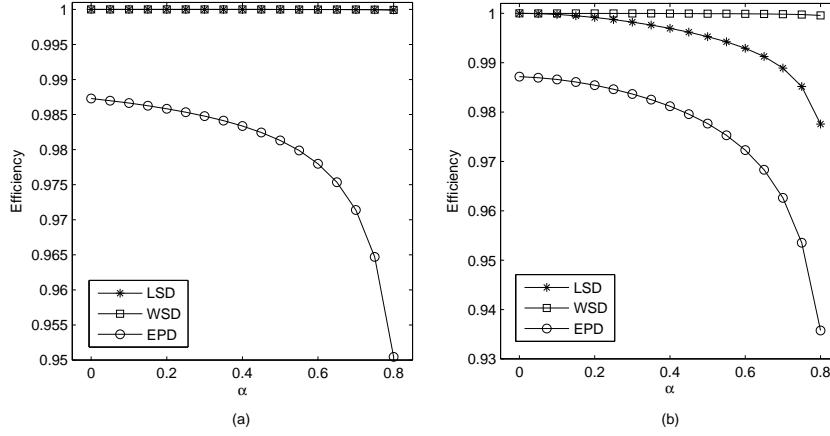


Figure 1: Efficiency plots of designs computed for a uniform prior under the reduced model (a) exchangeable correlation structure (CS) and (b) AR(1) correlation structure for Example 1

70% of weight. As α increases the first eight sequences get more than 90% weight with equal proportions. For the AR(1) structure, D^B again utilizes the first eight sequences with more than 70% of weight and the results do not change with α . It can be observed from Figure 2 that WSD is most efficient compared to LSD and EPD under both correlation structures. Efficiency of WSD reduces marginally with an increase in α , while efficiencies of the other designs decrease more as compared to WSD with α . Results are same when normal priors used.

5.2. Example 2: Two periods two treatments Poisson response trial

A crossover trial with two drugs given in two periods for controlling angina in 20 patients is considered. The count of attacks suffered by the patients is assumed to be a Poisson variable. Treatment sequences AB and BA are used in the trial. However, we should note that this design does not permit the unbiased estimation of the treatment contrast under carryover effect (Jones and Kenward (2014)), though the estimates and corresponding confidence intervals may still be used to choose the prior distributions.

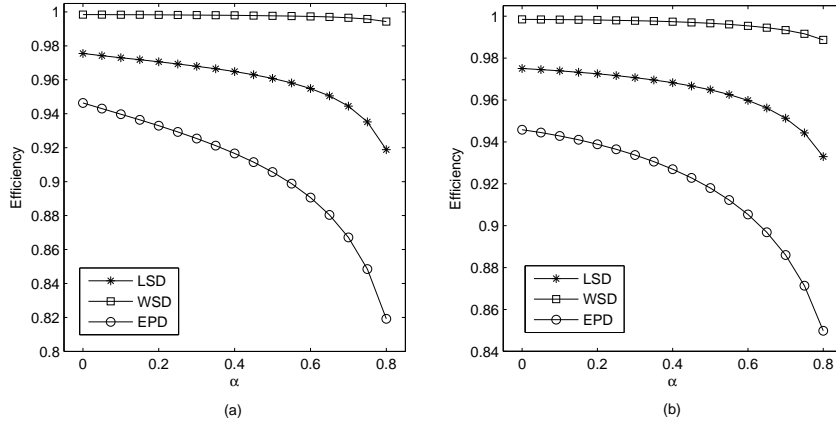


Figure 2: Efficiency plots of designs computed for a uniform prior under the full model (a) exchangeable correlation structure (CS) and (b) AR(1) correlation structure for Example 1

The linear predictor η_{ij} for this 2×2 crossover design is,

$$\eta_{ij} = \mu + \beta P + \tau T + \rho C,$$

where P, T and C are the indicator variables for the period, direct treatment and crossover effects, respectively. For a 2×2 cross-over trial compound symmetric and AR(1) correlation structures are equal. Estimation of the parameters is again done by using *PROC GENMOD* in SAS software Inc. (1999). Point estimates and their 95% confidence intervals are listed in Table 3. Estimate of the correlation coefficient is $\alpha = 0.0798$.

Table 2: Point estimates and confidence intervals for Poisson data in Example 2.

Parameter	Point estimate [95%Confidence interval]	
	no carryover effect	with carryover effect
μ	0.0493 [-0.4457 0.5444]	-0.0541 [-1.0405 0.9324]
β	-0.0011 [-0.4256 0.4234]	0.0541 [-0.4519 0.5600]
τ	0.5664 [0.1006 1.0322]	0.6419 [-0.1036 1.3873]
ρ	-	0.1494 [-0.8566 1.1553]

For finding the Bayesian crossover designs we search over the space of all treatment sequences, $\{AB, BA, AA, BB\}$. The Bayesian design with the D -optimal allocation of subjects to the treatment sequences $\{AB, BA, AA, BB\}$ is denoted by D^B . The performance of D^B is compared to $D_I = \{AB, BA\}$ with equal allocation to each sequence, and another design D_{II} with treatment sequences $\{AB, BA, AA, BB\}$, but with equal allocation to each treatment sequence. The parameter space \mathcal{B} is similarly chosen for both uniform and normal priors as in Example 1. The results of the design comparisons is given as efficiency plots in Figure 3.

5.2.1. Reduced model: No carryover effects

For all values of α , the Bayesian crossover design D^B for the reduced model consists of sequences $\{AB, BA\}$ with approximately equal proportion of subjects to each sequence, thus D_I and D^B are similar under the reduced model. However, the performance of D_{II} is affected by increasing values of the correlation parameter. The results matches with that of the normal response model for a 2×2 crossover design (Laska and Meisner (1985)).

5.2.2. Full model: With carryover effects

Introducing crossover effects in the model, however changes the results completely. The Bayesian crossover design D^B for full model utilizes the sequences $\{AA, AB\}$ and its dual

with approximate equal proportion of subjects to each sequence, thus D_{II} and D^B are similar under the full model, for all α . The original design D_I considered in the trial has very low efficiency compare to D^B and is also affected by increasing α . This result again matches that of a normal response with carryover model, where treatment sequences $\{AA, AB, BB, BA\}$ with equal proportions of the subjects are optimal for estimating treatment contrasts (Laska and Meisner (1985)).

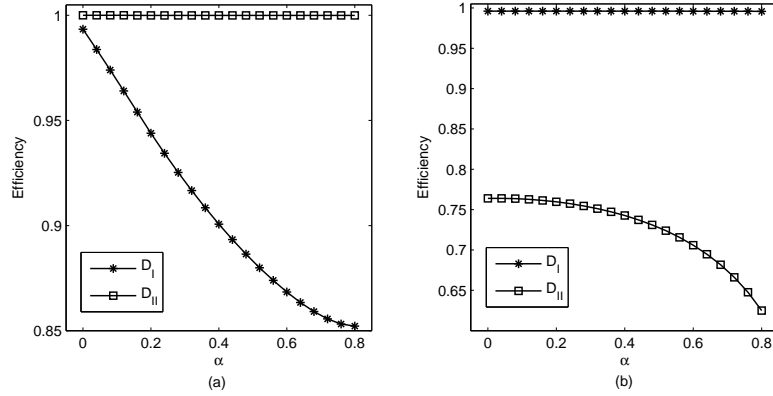


Figure 3: Efficiency plots of designs computed under a uniform prior for (a) reduced model (b) full model for Example 2

5.3. Example 3: Three periods two treatment Gamma response trial

We consider a hypothetical gamma response trial with two treatments, A and B applied in three periods. The response is length of hospital stay which is assumed to follow a Gamma distribution. The Bayesian crossover design D^B is determined by searching over the treatment sequences, $AAB, ABB, ABA, BBA, BAA, BAB$. Linear predictor for this crossover design is

$$\eta_{ij} = \mu + \beta_1 P_1 + \beta_2 P_2 + \tau T + \rho C$$

where P_i is again the indicator variable for i th period, T is the indicator variable for treatment and C is the indicator variable for carryover effect.

The data sets are simulated using the parameter values $(\mu, \beta_1, \beta_2, \tau) = (0.50, 0.15, 0.20, 0.25)$ for a reduced model and $(\mu, \beta_1, \beta_2, \tau, \rho) = (0.50, 0.20, 0.30, 0.25, 0.15)$ for a full model. We have considered the treatment sequences ABB and BAA with the assignment of 10 subjects each to generate the data. Observations are assumed to be independent within the periods. The link function used is defined in Section 3.4 and the shape parameter κ is fixed at 2.0. The point estimates and the confidence intervals listed in Table 5 are used to create the parameter space, \mathcal{B} , for both the normal and uniform priors. We compared the Bayesian D -optimal design D^B with the following designs:

$D_a = ABB, BAA, AAB, BBA$ with equal allocation to each treatment sequence.

$D_b = ABB, BAA$ with equal allocation to each treatment sequence.

$D_c = ABA, BAB, ABB, BAA$ with equal allocation to each treatment sequence.

Table 3: Point estimates and confidence intervals for Gamma response in Example 3.

Parameter	Point estimate [95% Confidence interval]	
	no carryover effect	with carryover effect
μ	0.5455 [0.3590 0.7321]	0.3674 [0.2135 0.5213]
β_1	0.1567 [0.0433 0.3567]	0.2271 [-0.0547 0.5089]
β_2	0.14 [-0.2324 0.2592]	0.2498 [0.0245 0.4751]
τ	0.1724 [0.0065 0.338]	0.1134 [-0.1335 0.3603]
ρ	-	0.1477 [-0.1621 0.4575]

5.3.1. Reduced model: No carryover effects

First we consider the uniform prior distribution for the parameters. Under independent correlation structure ($\alpha = 0$), Bayesian D -optimal design D^B utilizes all the sequences

$\{AAB, ABB, ABA, BBA, BAA, BAB\}$ with the proportions of (21%, 12%, 21%, 13%, 21%, 13%) to each sequence. From Figure 4 for $\alpha = 0$, it is noted that designs D_a , D_b and D_c are as efficient as D^B with efficiency approximately equal to 1.

Under the CS structure, D^B uses $\{AAB, ABA, BBA, BAA\}$ sequences with proportions (46%, 8%, 38%, 8%). As correlation increases (near $\alpha = 0.8$), D^B assigns almost (50%) proportions to each of the sequences $\{AAB, BBA\}$. Observing Figure 4 (a), design D_a turns out to be more efficient compared to D_b and D_c . Performance of all designs decrease as α increases also, designs D_b and D_c are quite similar in their efficiencies.

For the case of AR(1) structure, D^B utilizes the sequence ABA and its dual with equal proportions for all values of α . Design D_c is more efficient compared to D_a and D_b while D_b performs the worst. Results stay same for normal priors.

5.3.2. Full model: With carryover effects

Under independence correlation structure, D^B utilizes the sequences $\{ABB, AAB\}$ and their dual with approximately equal proportions. When a carryover effect is included in the model D^B utilizes the sequence ABB , AAB and their dual with approximately equal proportions for each α under CS correlation structure. Thus, D^B is similar to D_a . Under the AR(1) correlation structure, D^B utilizes the sequence ABB , AAB and their dual with approximately equal proportions for $\alpha < 0.2$, for $0.2 \leq \alpha \leq 0.5$, it gives about 70% weight to $\{AAB, BBA\}$, 28% to $\{ABB, BAA\}$ and includes BAB in the design. For higher values of α , D^B utilizes AAB and BBA with more than 80% weight and the rest goes to ABB and BAB .

From Figure 5 we see that the designs D_b and D_c perform badly when compared to D_a (similar to D^B) for all values of α and for both CS and AR(1) structures. The results remain unchanged to changes in the scale parameter value κ . Use of normal prior provides the same results. Under AR(1) correlation structures, Laska and Meisner (1985) reported similar observations for normal responses.

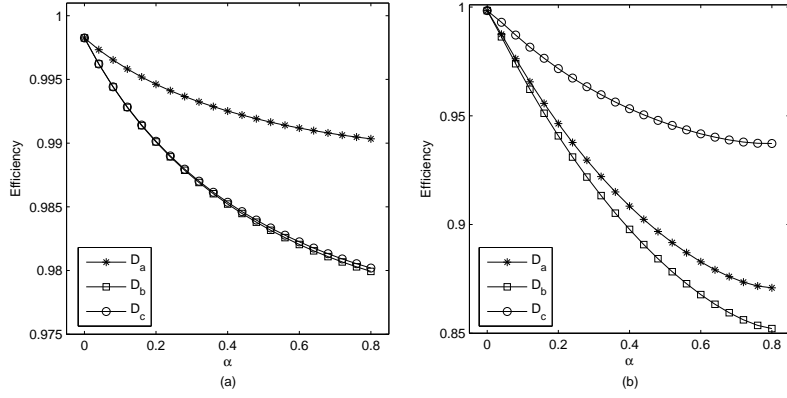


Figure 4: Efficiency plots of designs computed for a uniform prior for reduced model under (a) exchangeable correlation structure (CS) and (b) AR(1) correlation structure for Example 3

6. Concluding Remarks

Crossover designs are popular as designs of choice in many clinical and pharmaceutical trials for comparing treatments. However, very often in these situations the response does not follow the usual assumptions of normality, and generalized linear models have to be used to model the data. In this article, we address the designing of such crossover trials when a GLM is fitted. Since the designs are dependent on the model parameters, Bayesian designs are proposed. Comparing our main results based on GLMs with those of normal response models, we see that they are quite similar in many cases.

The main results on the estimation of direct effects using the proposed D-optimal Bayesian designs (D^B) are summarized below.

- **For $t = p = 4$ when the response is binary :** Williams design is as efficient as D^B and is seen to perform the best under both CS and AR(1) correlation structures for a reduced as well as a full model.

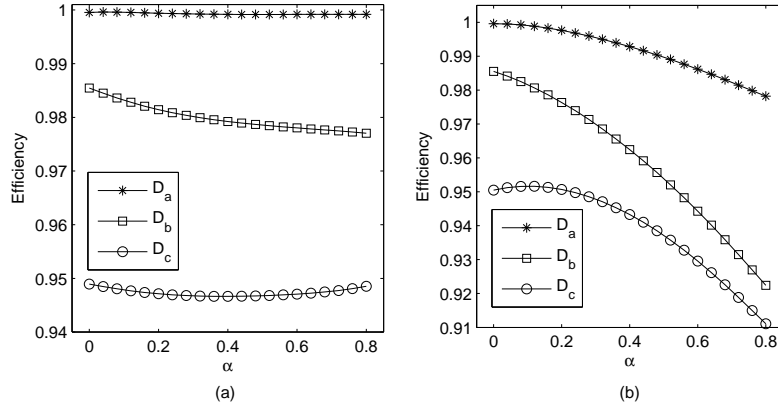


Figure 5: Efficiency plots of designs computed for a uniform prior for full model under (a) exchangeable correlation structure (CS) and (b) AR(1) correlation structure for Example 3

- **For $p = t = 2$ when the response is Poisson distributed:** Design $\{AB, BA\}$ has the highest efficiency in a reduced model framework while for a full model, design $\{AB, BA, AA, BB\}$ is most efficient. Both designs have equivalent efficiency as D^B for the respective models.
- **For $p = 3, t = 2$ when the response is Gamma distributed:** For a reduced model, design $\{AAB, ABA, BBA, BAA\}$ is the D -optimal Bayesian design under CS structure for correlation $\alpha < 0.6$. While for higher values of α , design $\{AAB, BBA\}$ is the D -optimal Bayesian design. For AR(1) correlation structure, design $\{ABA, BAB\}$ turn out to be the D -optimal Bayesian design. While for a full model, under CS structure, design $\{ABB, BAA, AAB, BBA\}$ is the D -optimal Bayesian design. Under AR(1) correlation structure, D^B is same as in case of CS structure for $\alpha < 0.2$, but for $0.2 \leq \alpha \leq 0.5$, it gives more proportions (70%) to AAB and BBA . For higher values of α , D^B utilizes AAB and BBA with more than 80% weight and rest to $\{ABB, BAB\}$.

In many biological experiments while studying the effect of drugs, the response measured

may not be binary in nature but say ordinal. As an example consider a 3×3 crossover trial (cited by Jones and Kenward (2014)) where the effect of three treatments on the amount of patient relief is studied. The response obtained is categorized as none, moderate or complete, making it ordinal in nature with three categories. Thus, there is a need to address optimal crossover designs not just for binary models but also for multi categorical responses. In these cases, instead of the logit link, a generalized logit or a proportional odds model may be used. Also, other than the correlation between measurements from the same subject we would have to consider the relation between response categories. Jones and Kenward (2014) discusses modeling of ordinal data using the GEE approach. In future, we are interested to study D-optimal Bayesian designs for such multicategorical models.

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